OIPE
DEC 16 1997
PATENT & TRADEMARK OFFICE

#19

DOCKET NO.: 91875J

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	William McBride, et al.		
SERIAL NO.:	08/253,973	EXAMINER:	M. Hartley
FILING DATE:	June 3, 1994	GROUP:	1311
TITLE:	**MONOAMINE, DIAMIDE, THIOL-CONTAINING METAL CHELATING AGENTS**		

Box AF
Assistant Commissioner of Patents
Washington, D.C.

Sir:

DECLARATION PURSUANT TO 37 C.F.R. 1.132

In support of the above-identified application, John Lister-James states the following.

1. I received my B.Sc., with honors, in chemistry from Imperial College of the University of London in 1974, and I was awarded my Ph.D. in organic chemistry from the University of London in1981. From 1981 to 1986 I was a Research Fellow in the Nuclear Medicine Department of Children's Hospital, Boston, MA. During the same time period I was a Visiting Scientist at the Massachusetts Institute of Technology, Cambridge, MA. From 1983 to 1986, I was also an Associate in Radiology in the Nuclear Medicine Department of Harvard Medical School. During this period, my research included designing, synthesizing and modifying ^{99m}Tc radiopharmaceuticals; investigation of structure/activity relationships probing biochemical processes; and development of new methods in organic synthesis. From 1987 to 1990, I was employed

at Centocor, Inc., Malvern, PA, in the Radiopharmaceutical Research & Development Department, in a variety of senior positions. At Centocor, Inc., I supervised the product development support for, wrote sections of, and coordinated the completion of the technical sections of US and European Product License Applications for a radioimmunodiagnostic product. While at Centocor, I also supervised technical projects supporting Product License Application submissions, and I supervised a group of senior and associate scientists in the development of novel protein modification and radiolabeling methods leading to proprietary technology. I have been employed at Diatide, Inc., the assignee of the present application, since 1990, and I am currently Senior Director, Research and Development. I am a coauthor of numerous scientific publications, including the following:

1. Holman BL, Jones AG, Lister-James J, Davison A, Abrams MJ, Kirshenbaum, JM, Tumeh SS, English, RJ., A New ^{99m}Tc-Labeled Myocardial Imaging Agent, Hexakis (t-Butylisonitrile)-Technetium (I) [^{99m}Tc TBI]: Initial Experience in the Human. J Nucl Med. 25:1,350-1,355 (1984).
2. Brenner D, Davison A, Lister-James J, Jones AG., The Synthesis and Characterization of a Series of Isomeric Oxotechnetium (+5) Bisamido Bisthiolates. Inorg Chem. 23:3793-3797 (1984).
3. Holman BL, Sporn V, Jones AG, Sia STB, Perez-Balino N, Davison A, Lister-James J, Kronauge JF, Mitta AEA, Camin LL, Campbell S, Williams SJ, Carpenter AT. , Myocardial Imaging with Technetium-99m CPI - Initial Experience in the Human. J Nucl Med. 28:13-18 (1987).
4. Piwnica-Worms D, Kronauge JF, Holman BL, Lister-James J, Davison A, Jones AG., Hexakis (carbomethoxyisopropyl-isonitrile)technetium(I), a New Myocardial Perfusion Imaging Agent: Binding Characteristics in Cultured Chick Heart Cells. J Nucl Med. 29:55-61 (1988).
5. Bryson N, Dewan JC, Lister-James J, Jones AG, Davison A. , Neutral Technetium(V) Complexes of Amide Thiol Thioether Chelating Ligands. Inorg Chem. 27:2154-2161 (1988).
6. Bryson NJ, Brenner B, Lister-James J, Jones AG, Dewan JC, Davison A. , Synthesis and Molecular Structure of a "Lantern" Dimer AsPh4)2[Tc202(SCH2CONHCH2CH2NHCOCH2S)4]. Inorg Chem. 28:3825-3828 (1989).
7. Bryson N, Lister-James J, Jones AG, Davis WM, Davison A., Protecting Groups in the Preparation of Thiolate Complexes of Technetium. Inorg Chem. 29:2948-2951 (1990).
8. Weber RW, Boutin RH, Nedelman MA, Lister-James J, Dean RT., Enhanced kidney clearance with an ester-linked ^{99m}Tc-radiolabeled antibody Fab'-chelator conjugate. Bioconjugate Chem. 1:431-437 (1990).
9. Moyer BR, Vallabhajosula S, Lister-James J, Bush LR, Cyr JE, Snow DA, Bastidas D, Lipszyc H, Dean RT., Technetium-99m-White Blood Cell-Specific Imaging Agent Developed from Platelet Factor 4 to Detect Infection, J. Nucl Med 37:673-679 (1996).

10. Vallabhajosula S, Moyer BR, Lister-James J, McBride BJ, Lipszyc H, Lee H, Bastidas D, Dean RT, Preclinical Evaluation of Technetium-99m-Labeled Somatostatin Receptor-Binding Peptides. J. Nucl Med 37:1016-1022 (1996).
11. Pearson DA, Lister-James J, McBride WJ, Wilson DM, Martel LJ, Civitello ER, Taylor JE, Moyer BR, Dean RT., Somatostatin Receptor-Binding Peptides Labeled with Technetium-99m: Chemistry and Initial Biological Studies. J. Med. Chem. 39:1361-1371 (1996).
12. Pearson DA, Lister-James J, McBride WJ, Wilson DM, Martel LJ, Civitello ER, Taylor JE, Moyer BR, Dean RT., Thrombus Imaging Using Technetium-99m-Labeled High-Potency GPIIb/IIIa Receptor Antagonists. Chemistry and Initial Biological Studies. J. Med. Chem. 39:1372-1382 (1996).
13. Lister-James J, Knight LC, Maurer AH, Bush LR, Moyer BR, Dean RT., Thrombus Imaging with a Technetium 99m-Labeled, Activated Platelet Receptor-Binding Peptide. J. Nucl Med 37:775-781 (1996).

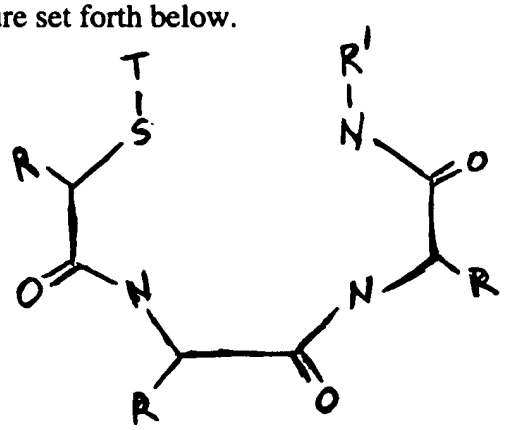
I am a coinventor of numerous issued U.S. patents, including the following:

U.S.Pat. No. 4,673,562, issued June 16, 1987, entitled Bisamide bisthiol compounds useful for making technetium complexes.
U.S.Pat. No. 4,746,505, issued May 24, 1988, entitled echnetium diagnostic fatty acids derived from bisamidebisthiol ligands.
U.S.Pat. No. 5,162,505, issued 1992, entitled Proteins m
odified with positively changed carriers and compositions prepared therefrom.
U.S.Pat. No. 5,185,433, issued February 9,1993, entitled Cross-linking protein compositons having two or more identical binding sites.
U.S.Pat. No. 5,225,180, issued July 6, 1993, entitled Technetium-99m Labeled Somatostatin-Derived Peptides for Imaging.
U.S.Pat. No. 5,508,020, issued April 16, 1996, entitled Technetium-99m Labeled Peptides for Imaging.
U.S.Pat.No. 5,645,815, issued July 8, 1997, entitled Radiolabeled Compounds for Thrombus Imaging.

2. I have read and understood U.S.Pat.No. 4,965,392 (Fritzberg et al.) and WO 93/12819 (Rhodes et al.), each of which has been cited against the claims now pending in the above-identified application.

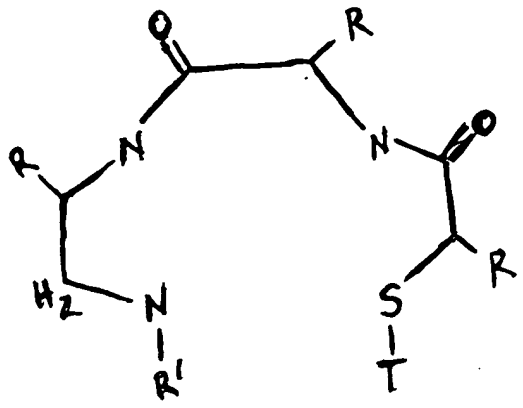
3. The only teaching of how to make the chelators of Fritzberg et al. is set forth at col. 8, lines 15-21, where Fritzberg et al. states that the chelators are synthesized from tripeptides such as glycylglycylglycine and S-protected esters of acetic acid. Fritzberg et al. does not disclose any other starting materials for synthesis of metal chelators, nor does

Fritzberg et al. disclose any other method for making metal chelators than addition of 2-thioacetic acid to tripeptides. If the starting materials disclosed in Fritzberg et al. are used, formula I appearing at col. 3, lines 8-34 of Fritzberg et al. is necessarily interpreted as having the structure set forth below.

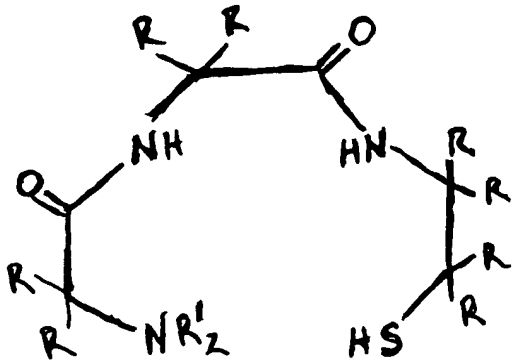


It is clear that the disclosure of Fritzberg et al. is enabling only for triamide/thiol chelators. Fritzberg et al. does not teach how to make a monoamine, diamide thiol-containing metal chelator, in which one of the "X" substituents of formula I is H_2 instead of a carbonyl group.

4. Even if Fritzberg et al. were considered to enable a monoamine, diamide thiol-containing metal chelator, when formula I of Fritzberg et al. is rotated and one X is substituted as H_2, as shown below, it can readily be seen that the formula of the present claim 2 differs substantially from formula I of Fritzberg et al.



In order to fit the backbone structure of formula I of Fritzberg et al., n, m, and p must be 0 in the formula of amended claim 2. When n, m, and p are 0, the formula of amended claim 2 becomes:



The metal chelators of amended claim 2 and its dependent claims clearly differ in structure from metal chelating compounds having formula I of Fritzberg et al.

5. A particular advantage of the presently claimed monoamine, diamide thiol-containing chelators is that they form a neutral complex with a metal ion such as an oxotechnetium (V) ion. When the reagent forms a neutral complex with a metal ion, the binding properties of the targeting moiety are substantially the same as those of the uncomplexed reagent.

From formula II of Fritzberg et al, which appears at col. 6, lines 1-11, it is clear that Fritzberg et al. does not contemplate a neutral complex between a metal ion and the metal chelating compounds disclosed therein. Formula II of Fritzberg et al. contrasts distinctly with formulae VIII, X and XII of the present application which appear at pages

16, 17 and 18, respectively. In formulae VIII, X, and XII the hydrogens of the amine are clearly shown as remaining when Tc (or any metal) is chelated, and inspection of the charge distribution in these formulae reveals that the chelate has an overall neutral charge. In Fritzberg et al.'s formula II, no hydrogens are shown on any of the nitrogens, and inspection of the charge distribution reveals that Fritzberg et al.'s chelates have an overall charge of -1 when oxotechnetium (V) or oxorhenium are chelated. In fact, all of the metal chelators disclosed in Fritzberg et al. form anionic complexes with metal ions.

6. Rhodes et al. contains no disclosure of a monoamine, diamide thiol-containing metal chelator. The $[Y_1-(R_1)-Y_1]$ formula discussed at page 5 of the Office Action dated November 13, 1996 cannot accurately be interpreted as a disclosure of a metal ion-binding domain having the amino acid sequence Lys-Cys-Arg.

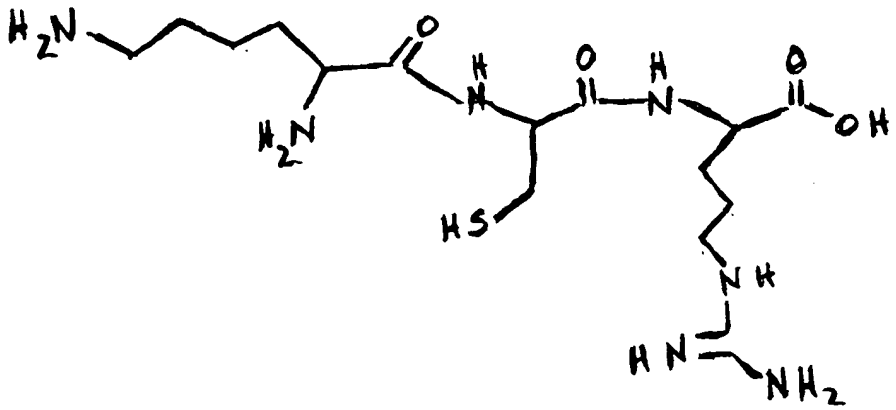
First, a term such as Y_1 is conventionally interpreted as representing the same chemical entity. The fact that Rhodes et al. also discloses a metal ion-binding domain having a formula $[Y_1-(R_2)-Y_2]$ supports a conventional interpretation of the formulae. Thus the formula $[Y_1-(R_1)-Y_1]$ simply would not conventionally be interpreted in such a way that Y_1 could be both Lys and Arg.

Nor can the formula $[Y_1-(R_2)-Y_2]$ be accurately interpreted to represent Lys-Cys-Arg. At page 11, line 35 to page 12, line 2 of Rhodes et al.[1] the range of possible substitutions of the generic formulae are explained. In the formulae of Rhodes et al., ". . .

[1] The same disclosure appears in the abstract; at col. 3, lines 44-62; and at col. 4, line 59 to col. 5, line 11 of U.S.Pat.No. 5,443,816, cited in the Office Action dated June 16, 1997 at page 8.

Y_1 and Y_2 are amino acids comprising a sulfur, nitrogen or oxygen which is available for binding to metal ions, or can be made available for binding to metal ions." R_2, if it does not comprise the biological function domain of the peptide, comprises ". . . an amino acid sequence containing from 0 to about 20 amino acids." No specific disclosure of a monoamine, diamide thiol-containing metal ion-binding domain appears in Rhodes et al. In fact, the only specific disclosures of metal ion-binding domains appears at col. 4, lines 7-28; at col. 5, lines 24-44; at col. 10, lines 36-60; at col. 15, lines 15-63; at col. 18, line 51 to col. 19, line 35; in the Examples; in the sequence listing; and in the claims. None of these disclosures supports a Lys-Cys-Arg or a monoamine, diamide thiol-containing metal ion-binding domain configuration.

7. In fact, when the structure of Lys-Cys-Arg is drawn out, as indicated below, it is readily apparent that no monoamine, diamide, thiol-containing metal chelating structure can possibly be formed.



I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Signed: _____
John Lister-James

Dated 15 Dec 97